

## **REMARKS**

### **Introductory Matter**

Applicants acknowledge, with appreciation, the Examiner's reconsideration of the restriction requirement and statement that Groups IX and X will be considered together.

### **THE AMENDMENTS**

Claims 6-9 and 20-21 are pending in this application. Claims 1-5 and 10-19 are withdrawn. Following entry of this amendment, claims 6-9 and 20-21 will be pending.

Applicants have amended specification pages 2 and 76 to insert the appropriate application numbers.

Applicants have amended the description of Figures 4-7 in the Brief Description of the Drawings section of the application to insert sequence identifiers.

Applicants have amended claim 6 to cancel the recitation of "competent to refold under suitable conditions." Applicants have also amended claim 6 to recite that "the latent protein is a refolded protein." Support for this amendment can be found at, *e.g.*, specification page 69 lines 22-24.

Applicants have amended claims 7-9 to improve their form.

None of the amendments introduces any new matter.

## **THE OBJECTIONS**

### **Sequence Compliance**

The Examiner states that the application fails to comply with the requirements of 37 C.F.R. § 1.821-1.825 because not all the amino acid sequences in the specification and drawings have been identified with a SEQ ID NO. Specifically, the Examiner contends that the sequences set forth on pages 44 and 45 and Figures 4-7 have not been identified with a SEQ ID NO. Applicants traverse in part and amend in part.

First, applicants respectfully submit that the specification does recite the SEQ ID NOs for the sequences that appear on pages 44 and 45. The sequence provided on page 44 is the TGF- $\beta$  Subgroup Pattern. The SEQ ID NO for that sequence (SEQ ID NO 64) is provided on page 43 in the paragraph that immediately precedes the sequence. Similarly, the sequence provided on page 45 is the Vg/dpp Subgroup Pattern. The SEQ ID NO for that sequence (SEQ ID NO 65) is also provided in the paragraph immediately preceding the sequence.

Second, with respect to Figures 4-7, applicants have amended the Brief Description of the Drawings section for Figures 4-7 to reflect the appropriate SEQ ID NOs. Accordingly, applicants request that the Examiner withdraw this objection.

**The Specification**

The Examiner has objected to the specification stating that there are numerous blank spaces.

Applicants have amended specification pages 2 and 76 to replace the blank spaces with the appropriate information relating to the applications, thus obviating the objection.

**THE REJECTIONS**

**35 U.S.C. § 112, First Paragraph**

The Examiner has rejected claims 6-9, 20 and 21 under 35 U.S.C. § 112, first paragraph as containing subject matter which was not described in the specification in such a way as to reasonably convey to the skilled worker that the inventors at the time the application was filed had possession of the claimed invention. The Examiner contends that the claims encompass a genus of cleavable sequences operably linked to a genus of TGF- $\beta$  family protein C-terminal domains and that there is no requirement that the cleavable leader sequence possess any particular conserved structure or other distinguishing feature. The Examiner further contends that there is no description regarding how to choose a leader sequence, such as one from another TGF- $\beta$  family protein, to be used as a leader sequence that inhibits the biological activity associated with a TGF- $\beta$  family protein C-terminal domain. Applicants traverse.

Applicants respectfully submit that the specification provides adequate written description for the latent TGF- $\beta$  family member fusion proteins recited in the claims. The specification at pages 77-79 discloses various latent TGF- $\beta$  fusion protein. For example, at page 77, the specification discloses latent fusion proteins wherein the leader sequence is a collagen binding domain, an FB domain of protein A or a hexahistidine region. The specification discloses that these fusion proteins display little or no activity in a ROS assay but are activated upon cleavage of the N-terminal non-morphogen peptide to yield an active C-terminal morphogen domain. Figure 7A-J and pages 79-82 describe various such fusion proteins. Applicants submit that this disclosure provides the requisite written description for the latent TGF- $\beta$  fusion protein recited in the claims. Accordingly, applicants request that the Examiner withdraw this rejection.

**35 U.S.C. § 112, First Paragraph**

1. The Examiner has rejected claims 6-9, 20 and 21 under 35 U.S.C. § 112, second paragraph for being indefinite. Specifically, the Examiner contends that claim 6 recites "refold under suitable refolding conditions" but that the specification fails to define the conditions unambiguously.

Applicants traverse. However, solely in the interest of expediting prosecution of this application, applicants have amended claim 6 to cancel the recitation that the latent protein is "competent to refold under suitable refolding conditions." Claim 6 has also be amended to recite that the latent protein is a refolded protein.

2. The Examiner contends that claim 7 recites "wherein a tissue-targeting domain is embedded within said cleavable leader sequence" but that recitation contradicts the limitation "whereby cleavage of the leader sequence will not cleave said tissue-targeting domain from said C-terminal domain."

Applicants traverse. Applicants respectfully submit that claim 7 is not unclear. The two portions of the claim identified by the Examiner are not contradictory. Claim 6 from which claim 7 depends, recites that the C-terminal domain becomes active upon cleavage of *a part* or all of said leader sequence. Therefore, claim 7 recites fusion proteins whereby only that portion of the leader sequence that does not include the tissue targeting domain is cleaved.

For all the above reasons, applicants request that the Examiner withdraw the indefiniteness rejection.

35 U.S.C. § 102(b)

The Examiner has rejected claim 6 under 35 U.S.C. § 102(b) as being unpatentable over WO91/05565 ("Cohen"). The Examiner contends that Figure 2A and 2B of Cohen teach a fusion protein comprising a leader sequence and C-terminal domain and that the leader sequence can be cleaved at the Asp-Pro site in the hinge region with dilute acid or at the Asn-Gly site with hydroxylamine and the C-terminal domain becomes active after refolding. Applicants traverse.

Applicants submit that Cohen does not anticipate claim 6. First, claim 6 recites a latent TGF- $\beta$  family member fusion protein wherein the protein comprising *both the TGF- $\beta$  family protein and the leader sequence is a refolded protein*. Cohen, in contrast discloses a protein which is *refolded after the leader sequence is cleaved* (see Cohen page 21, section entitled "3. Production of Active Analogs"). Thus, Cohen does not disclose a refolded protein comprising both the TGF- $\beta$  member protein and the leader sequence as is recited in claim 6 of the instant application.

Second, claim 6 recites a latent TGF- $\beta$  family member fusion protein, comprising a TGF- $\beta$  family protein C-terminal *seven cysteine domain*, comprising a finger 1 subdomain, a finger 2 subdomain, and a heel subdomain. Figures 2A and 2B of Cohen disclose fusion proteins having either the *6-cysteine domain* or *8 cysteine domain* of TGF- $\beta$ 1. They do not disclose fusion proteins having a *seven cysteine domain*.

For all the above reasons, Cohen does not anticipate claim 6. Accordingly, applicants request that the Examiner withdraw the rejection.

### Claim Objections

The Examiner has objected to claims 6-9 stating that they recite non-elected subject matter (TGF- $\beta$  family proteins).

Applicants note that claims 6-9 are generic with respect to the TGF- $\beta$  family proteins and that they elected the species OP-1 for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable.

**CONCLUSION**

In view of the foregoing remarks and amendments, applicants request that the Examiner favorably reconsider this application and allow the amended claims pending therein. Should the Examiner feel that a telephone conference with applicants' representatives would assist the Examiner, she is invited to telephone the undersigned at any time.

Respectfully submitted,

/ KAREN MANGASARIAN /

---

James F. Haley, Jr. (Reg. No. 27,794)  
Karen Mangasarian (Reg. No. 43,772)  
Attorneys for Applicants

ROPES & GRAY LLP  
Customer No. 1473  
1211 Avenue of the Americas  
New York, New York 10036  
Tel.: (212) 596-9000  
Fax: (212) 596-9090